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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/293,670	04/16/1999	JOSEPH FISHER	A-68104/DJB/	5176

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FOLEY HOAG, LLP
PATENT GROUP, WORLD TRADE CENTER WEST
155 SEAPORT BLVD
BOSTON, MA 02110

EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 02/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/293,670	FISHER ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/8/2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-36* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-26, 30 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 26 (in part), 27-29. 31, 32 (in part) and claims 33-36 .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 17-32 in the reply filed on 09/08/2005 is acknowledged. The traversal is on the ground(s) that the method claims in Group II may be practiced using certain of the species that are defined in the method claims of Group 1. Further, Applicants respectfully assert that simultaneous examination of Groups I and II would not place an undue burden on the Examiner because the claims of the two Groups in certain embodiments would involve certain similar steps. This is not found persuasive because Group II as stated by applicants cover a broader scope than Group I (which was not originally examined in the prior Office action). Thus, examination of a broader scope (not originally examined) would impose undue burden of examination as to the numerous cells encompassed by Group II.

The requirement is still deemed proper and is therefore made FINAL.

Applicants' election of the species annexin granule binding from subgroup A, the species peptide, from subgroup B, and the species p21, from subgroup C is noted. It is Applicants' position that while a species election may be proper in each case among the species of each Subgroup for prosecution on the

merits to which the claims shall be restricted if no generic claim is finally held to be allowable, an election under 35 U.S.C. 121 is improper if the claims reciting the various species are linked by an allowable generic linking claim (see M.P.E.P. 809.02). For example, claim 17 requires that the method comprise sorting said population of cells based on at least five parameters using fluorescence activated cell sorting. (FACS), the species of which genus are recited in dependent claim 26. Further, claim 17 requires that the method comprise a population of retrovirally infectable cells comprising a library of retroviral vectors encoding different candidate bioactive agents, wherein the various species of bioactive agents are recited in dependent claims 30-32. Finally, claim 32 provides that the method of claim 17 additionally comprise a positive control, which may be selected from the recited species. Applicants should be restricted to a single species for search purposes only. It is Applicants' understanding that the search will be extended to the remaining species of each Subgroup upon a finding of allowability, and that the non-elected species of each Subgroup will be rejoined upon a finding that the generic claims linking them are allowable. Further, Applicants submit that for claim 32 reciting a Markush group of species that may serve as a positive control, the members of the Markush group

are sufficiently few in number and so closely related that a search and examination of the entire claim can be made without serious burden. Accordingly, Applicants further traverse the species election for Subgroup C on the grounds that the Examiner has improperly restricted the Markush group reciting the species (see M.P.E.P. 803.02).

In response, as correctly stated by applicants, the search and examination of the other species would be extended only upon a finding of allowability of the elected species. With respect to claim 32, although the species are few in numbers however, the species are not structurally related as mutants cover numerous mutations of the p21 native molecule.

Status of Claims

Claims 17-36 are under examination.

Claims 26 (in part), 27-29. 31, 32 (in part) and claims 33-36 are withdrawn from consideration as being directed to non-elected inventions and species.

Claims 17-26, 30 and 32 (with respect to the elected species) are under examination.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-26, 30 and 32, as amended, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method specific for the p21 as the bioactive agent that modulates a specific tumor cell, does not reasonably provide enablement for a method using a library of any bioactive agents that modulates any population of cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons advanced in the last Office action of 1/10/2005.

Response to Arguments

Applicants note that the express purpose of the present invention is to evaluate whether or not a candidate bioactive agent alters a cellular phenotype by introducing it into the cells via a retroviral vector or by combining the cells with it, and analyzing the cells for phenotypic changes via at least five FACS parameters. The Examples serve to demonstrate proof of principle whereby a candidate bioactive agent (i.e., p21) was tested using the method of the invention to determine whether or not it alters the phenotype of the cells into which it was introduced, as detected by at least five FACS parameters. The intention of selecting p21 as the "candidate bioactive agent" was that its properties as a cell-cycle inhibitor (see page 16, lines 14-15) were known and expected to produce the phenotypic changes detected by the parameters described in Examples 1-12, as proof that the instantly claimed invention works, e.g. that at least five FACS parameters could be used to detect the phenotypic changes in a cell retrovirally transfected with a bioactive agent. The specification provides ample guidance as to how the teachings of the Examples may be modified for use in other cell types using other candidate bioactive agents.

In reply, applicants' arguments are unclear. Does the method require a known agent for the five-parameter analysis?

There is nothing in the claims that recite for a known candidate bioactive agent or which bioactive agent from the known ones are candidates agents that possibly exhibit the five-parameter factors.

Applicants argue that the invention is limited to a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents wherein the cells are retrovirally infectable. Applicants have amended claim 17 to require that the cells be "retrovirally infectable" to clarify that the types of cells to be used in the method must be infectable with a retroviral vector.

In response, applicants' arguments are unclear as all cells would appear to be retrovirally infectable, since the claims do not preclude or recite the ones that are or are not. For those that are not retrovirally infectable, the specification fails to teach said cells.

Applicants argue that the method of introducing agents using retroviral vectors into a variety of retrovirally infectable cell types; transfecting of cells, preparing of library are all well-known in the art at the priority date of the present application. Applicants further recite different sections in the specification that teaches said method.

In reply, these methods have been employed in the art utilizing specific components therein. No generalization(s) in any prior art has been made as to its applicability to a huge scope, as the claimed method. Applicants have not provided any evidence to the contrary. If applicants choose to rely on the knowledge in the prior art to render his disclosure enabling for the broad claim method applicants must show that anyone skilled in the art would have actually possessed the knowledge, In re Lange (CCPA 1981) 644 F2d 856, 209 USPQ 288. However, not everything which may be cited as prior art to preclude the grant of a patent can be equated with common knowledge for the purposes of meeting the enablement requirement of 112. Furthermore, a review of the relevant sections e.g., page 16, line 8 up to page 30, line 15 provides only a definition for the term "candidate bioactive agent". That is any molecule, e.g., protein, small organic molecule, carbohydrates (including polysaccharides), polynucleotide, lipids, etc. Applicants' disclosure would not enable a skilled artisan to carry out the claimed methods without undue experimentation given only the broad definitions of the components used in the method. It is not apparent which of these broad components can be combined or employed in the method to accomplish the claimed method.

Applicants argue that the "unpredictability" of the effect of the agents on the phenotype of the cell, or the screening or determining as whether a bioactive agent is a candidate for cell population reaction are irrelevant to the enablement analysis. Applicants strongly urge the Examiner, as we urged in our previous response to the prior Office Action, that the Patent Office has recognized screening assay claims having no limitation as to the compounds to be tested (see, e.g., U.S. Patent No. 6,461,813) and that this invention should be similarly treated.

In response, it is the scope of the enabling disclosure for the broad scope of the claims that is at issue that is not enabled. Furthermore, as stated in the last Office action, each application is treated on its own merits.

Applicants agree with point 3 on page 5 of the Office action that "the consequences of some bioactive agents and cell interaction on some cells have not been fully determined or elucidated." Applicants submit that this point underscores the purpose of the current invention. More specifically, the function of the methods of the present invention is to determine the effect of such compounds on cellular phenotypes.

In reply, a single embodiment of a known single component use in the method, not even a library, is not an underscoring of

the purpose of the invention. It is not seen how such consequential determination is made based on the broad scope of the claimed method with e.g., a library of undefined bioactive agents encoded by a retroviral vectors.

Applicants remind the Examiner that the scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. M.P.E.P. 2164.03.

In reply, this is recognized. In mechanical cases where there is little unpredictability the enabling disclosure of one species suffice. However, in a highly unpredictable art as e.g., cell phenotype alteration of gene, a single species would not suffice. While applicants are not required to disclose every operable species however, a reasonable assurance or a number of species as representative of the genus is required. In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

Applicants argue that simply because a large amount of work might be required to prepare a library of retroviral vectors in a retrovirally infectable cell type different from those in the Examples does not mean undue experimentation is involved.

In reply, preparing a library of retroviral vectors is but one of the numerous undefined parameters of the broad method.

There is the kind of cell that is altered by a bioactive agent(s), the type of phenotype caused by a particular or all agents and other numerous undefined factors of the claims.

Applicants argue that Example 1 successfully demonstrates proof of principle regarding the ability of the FACS to allow multiparameter detection of the effect of a compound on a cell's phenotype in relation to cell cycle analysis. Applicants state that it is the objective of the instant invention to identify agents which can affect a cellular phenotype as accessed by FACS. No prior knowledge is needed of the agents - the point is to test whether or not they would affect a cellular phenotype.

In response, this is contrary to the disclosure's showing and applicants' arguments of using a prior known bioactive agent, p21, that affect a cell's phenotype.

New Matter Rejection

Claim 32 which recites that a positive control is a fragment or mutant or mutant fragment of p21 is not supported in the as-filed specification. Applicants cite page 16, line 8 up to page 19, line 36 and the Examples. A review of these cited sections do not recite a mutant, fragment or mutant fragment of p21.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19, 25-26 and 32, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 19, "said fusion partner" lacks antecedent basis of support from the base claim 17. It is unclear as to which partner it is fused thereto.

B. Claim 25 is unclear and inconsistent with the base claim recitation of at least 5 parameters for sorting the cell populations.

C. Claim 26 is unclear as to whether these are different species of the parameters recited in claim 17 or the five-parameter itself.

D. Claim 32 is indefinite as to how the positive control is used in the base method especially for a mutant or fragment of a mutant.

Double Patenting

Claims 17-26, 30 and 32,as amended, are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of Application No. 09/157,748 (now U.S. Patent No. 6,461,813) or over application S.N. 09/062,330 for reasons of record.

Response to Arguments

Applicants state that at such time as the subject matter of the provisionally rejected claims is allowed in the '330 or '748 applications, Applicants will terminally disclaim the corresponding claims of the present application.

In reply, in the absence of a terminal disclaimer, the rejection is maintained.

Claims 17-26, 30 and 32, as amended, are rejected under 35 U.S.C. 103(a) as being obvious over Application No. 09/157,748 (now U.S. 6,461,813) which has a common inventor with the instant application for reasons advanced in last Office action.

Response to Arguments

Applicants traverse the foregoing rejection. However, at such time as the subject matter of the instant application is indicated allowable, Applicants will consider submitting a 37 C.F.R. 132 declaration to overcome the Examiner's rejection within the appropriate time frame.

In response, in the absence of the 132 declaration the rejection is maintained.

Claim Rejections - 35 USC § 103

Claims 17-25, 30 and 32, as amended, are rejected under under 35 U.S.C. 103(a) as being obvious over Nolan (WO 97/27212) in view of Jia-ping (Chinese Journal of Physical Medicine) or Ryan et al (Jrnl. of Immunological Methods) for reasons set forth in the last Office action.

Response to Arguments

Applicants state that even if a combination of prior art references teaches or suggests all of the claim limitations, no prima facie case of obviousness may be established without a motivation to combine. There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. The level of skill in the art cannot be relied upon to provide the motivation to combine references. The Examiner has not set forth any motivation to combine these references and hence has not established a prima facie case of obviousness. Moreover, even if there were motivation to combine the references, the combination does not teach or suggest each and every element of

the claims. The Examiner points out that Nolan discloses a method of screening for a bioactive agent capable of altering a cellular phenotype of a cell which comprises combining at least bioactive agent and a population of cell or introducing a library of nucleic acids encoding a candidate bioactive agents into a population of cells and sorting said cells in a FACS machine by separating said cells on the basis of at least three cellular parameters. However, Applicants note that Nolan fails to disclose or suggest the use of at least five parameters in the FACS sorting protocol as required in the instantly claimed invention. Further, Nolan does not disclose or suggest exocytosis as one of the measurable cellular phenotypes. Neither Jia-ping nor Ryan cures the deficiency of the Nolan disclosure. Applicants acknowledge that Jia-ping discloses the use of FACS, and specifically in relation to determining the cellular phenotype of exocytosis. Applicants acknowledge that Ryan discloses the use of FACS in connection with multiparameter sorting protocols. But argue that neither Jia-ping or Ryan discloses or suggests the use of at least five parameters in the FACS sorting protocol. Jia-ping, despite an initial statement that five parameters may be used, only discloses and enables four parameters: forward scattering, 90 scattering, fluorescence

1 and fluorescence 2. No fifth parameter is named or described. Ryan discloses only two parameters: log 90 scattering and red fluorescence. Further, there is no teaching or suggestion in either Jia-ping or Ryan that their teachings be combined with the teachings of Nolan, e.g. that the cells of Nolan could be analyzed using the particular FACS protocols described in Jia-ping and Ryan.

In reply, attention is drawn to Nolan's disclosure Example 1, line 23 up to page 52, line 2 which discloses measurement of five parameters. Example 1, page 51 uses FACS to analyze a fluoresceinated cell, expression of the cells, apoptosis inhibition, use of dye techniques as propidium iodide or other dyes such as ethidium bromide/acridine orange. Furthermore, Nolan at page 33, lines 19-28 Nolan describes that once a cell with an altered phenotype is detected, the cell is isolated from the plurality, which does not have altered phenotypes. This is done in any number of ways, as is known in the art, and will in some instances depend on the assay or screen. Suitable isolation techniques include FACS, expression of survival protein, (cell cycle, as claimed) induced expression of a cell surface protein(expression of a cell surface receptor, as claimed) or other molecule that can be rendered fluorescent or taggable for

physical isolation, death of cells (apoptosis) and isolation of DNA or other cell viability indicator dyes etc.

Thus, this suggested teachings of Nolan of the different means by which a cell phenotype can be detected or sorted can suffice the finding of obviousness. Each of Ryan and Jai-ping provides the motivation i.e., the advantages in doing a multi-parameter analysis using at least five parameters, as suggested by each of these references, one of which is exocytosis. Furthermore, while Nolan does not positively recite said exocytosis as the cellular phenotype however, it is considered that the process of Nolan is obviously an exocytosis since cellular excretion or discharge of a substance from the cell, occurs as a result of fusion of membranes. Applicants cannot show non-obviousness by attacking the references individually where the rejection is based on a combination of references. In re Young, 159 USPQ 725 (CCPA 1968). The test for obviousness under 35 USC 103 is not the express suggestion of the claimed invention in any or all of the references but what the references taken collectively would suggest; and inferences which one skilled it in the art would reasonably be expected to drawn from the disclosure in the references. In re Preda, 159 USPQ 342 and In re Conrad, 169 UASPQ 170. The fact that Jia-ping suggests measuring five parameters, four of which was described, as acknowledged by applicants,

would suffice the finding of obviousness. It would be within the ordinary skill in the art at the time the invention to pick and choose from the known and available parameters that can be combined to arrive at the claimed five parameters. Nolan discloses nearly the same process steps as claimed, except for the claimed exocytosis. This parameter as taught by Jia-ping and Ryan is known at the time the invention was made. Hence, the combined teachings of the prior art render the claimed prima facie obvious at the time of the invention.

Claim 32 is obvious over the disclosure of Nolan at page 37, last incomplete paragraph.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan in view of Hide et al(Jrnl. of Cell Biology) and applicants' disclosure of admitted art.

Nolan is discussed, above. Nolan further discloses at e.g., page 31, line 7 up to page 32, line 6 the FACS means of measuring the altered cellular phenotype except the claimed recitation that the exocytosis is measured by annexin granule binding. However, Hide discloses e.g., at page 488, col. 2 that cells (mast) contain large numbers of secretory granules which makes them highly refractile which is manifested in the light-scattering properties of the cells, particularly at around 90 degrees. When the cells have undergone exocytosis, their

refractivity is lost and their ability to scatter light at 90 degree is correspondingly diminished. This attribute has been used to classify populations of (mast) cells. Applicants at page 38, lines 10-20 admit that annexin is commercially available. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to measure the cellular phenotype alteration in the method of Nolan by exocytosis by annexin granule binding since exocytosis measured by granule binding is one of the means of classifying cell populations as taught by Hide (and appears to be a sensitive measure of the cell behavior as shown by its high refractile property).

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 27-29, 31 and 33-35 drawn to a non-elected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
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